Smell deficits as an endophenotype in patients with non-syndromic cleft lip and/or palate and their non-affected first-degree relatives: a pilot study

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Cleft lip and/or palate (CL/P) is one of the most frequent congenital birth defects with an incidence of 1/700 live births and a multifactorial etiology. Although recent studies such as linkage and association studies, have given insight in the genetic etiology of CL/P, most of the causal genes remain unidentified. A candidate gene approach, by the study of endophenotypes, is a unique and promising manner to reveal more of the genetic etiology of CL/P. Endophenotypes are characteristics that are associated with a condition and are considered to be an expression of the underlying susceptibility genes of this condition. One of the possible endophenotypes of CL/P is a higher frequency of olfactory dysfunction in patients and their non-affected first-degree relatives. Although olfactory function has not extensively been investigated in patients with non-syndromic CL/P, there is some evidence for a decreased capacity to smell in patients with CL/P and their non-affected relatives. Furthermore, olfactory dysfunction within syndromic CL/P could be an indication for reduced smell capacity within non-syndromic patients. When smell dysfunction is determined in non-affected relatives, it could be an indication for an underlying genetic cause.
In this pilot study with 48 patients, 41 non-affected relatives and 23 controls, smell capacity was tested using the Sniffin' Sticks (Burghardt), testing for smell threshold, discrimination and identification. Furthermore, a questionnaire for olfactory dysfunction was used to compare objective and subjective perception of the smell capacity. To confirm the central etiology of the smell deficits, an MRI was taken for volumetry of the olfactory bulb, expecting smaller olfactory bulb volumes in subjects with a decreased smell capacity. Structural defects were examined using acoustic rhinometry and rhinomanometry in subjects showing an olfactory deficit.
The pilot study revealed a significant olfactory dysfunction in patients with CL/P ($p=0.018$) and their non-affected relatives ($p=0.023$), compared to the control group. More olfactory dysfunction was seen in patients and relatives with a familial history of CL/P, indicating a genetic origin of this feature.
This study is the first to show decreased smell capacity in patients with CL/P and their non-affected first-degree relatives, indicating that olfactory dysfunction could be considered to be an endophenotype of non-syndromic CL/P.